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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,539	07/16/2003	H. William Bosch	029318-0961	6324

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EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1618	

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04/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/619,539	BOSCH ET AL.	
	Examiner	Art Unit	
	S. Tran	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-123* is/are pending in the application.

4a) Of the above claim(s) *46-123* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-45* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/18/08 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36, 38, 40, 42, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a stable nanoparticulate liquid dosage composition, does not reasonably provide enablement for the specific pharmacokinetic profiles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP § 2164.01 (a)). These include: breadth of the claims; nature of the invention; state of the prior art; amount of direction provided by the inventor; the level of predictability in the art; the

existence of working examples; quantity of experimentation needed to make or use the invention based on the content of the disclosure; and relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

Breadth of the claims: are broad in the sense that they recite particles in a broad size range with no specific surface stabilizer, or specific osmotically active crystal growth inhibitor.

Amount of direction provided by the inventor: the present specification does not teach how to precisely achieve the claimed pharmacokinetic profiles given: first, the wide range of particle size, *e.g.*, less than 2000 nm; second, the multitude types of suitable surface stabilizer; and third, the multitude types of osmotically active crystal growth inhibitor. The specification also fails to teach if the same pharmacokinetic profiles, for example, the same AUC can be achieved with general all possible types of surface stabilizer, much less, in any ratios. Most importantly, it is noted that the present specification disclosed the pharmacokinetic profiles as a "*desirable* feature" (see page 17, lines 11-13). No further instruction and/or guidance of directions as to how these specific profiles can be obtained. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. As such, the practitioner would turn to trial and error experimentation in order to compose a composition with multitude types of surfactants and crystal growth inhibitor in any amount or ratios to result in the claimed pharmacokinetic profiles, without guidance from the specification or the prior art.

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Claim Rejections - 35 USC § 102

Claims 1-3, 8-10, 12, 14-15, 17, 21-24, 26-30 and 32-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Bagchi et al. US 5,665,331.

Bagchi teaches a nanoparticle having average particle size less than 300 nm, the nanoparticle comprising pharmaceutical active agent, one or more surface stabilizers, and a crystal growth modifier (abstract; column 3, lines 16-62; and column 6, lines 49-55). Active agents include poorly soluble agent such as nsaid (column 5, lines 14-55). Active agents are in crystalline phase (column 5, lines 8-12). Surfactants are disclosed in column 6, lines 1-49). Additional surfactant is disclosed in column 6, lines 56-62). Surfactant is used in an amount ranging from 0.1-90% by weight based on the total weight of the dry particle (column 7, lines 1-5). Crystal growth modifier is used in an amount of between 1-40% by weight (column 11, lines 65-67). The obtained nanoparticles are suitable for the parenteral or oral administration in liquid dosage form (column 7, lines 6-51).

Bagchi does not expressly teach the pharmacokinetic profiles such as the AUC, Cmax, and Tmax. However, such limitations are inherent because Bagchi teaches the same nanoparticle comprising the same materials require by the present invention, namely, nanoparticle having average particle size less than 300 nm comprising a drug, a surface modifier, and a crystal growth inhibitor.

Claim Rejections - 35 USC § 103

Claims 1-4, 6, 8-24, 26-30 and 32-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge US 6,267,989, in view of Straub et al. US 2002/0142050 A1.

Liversidge teaches a method for preventing crystal growth and aggregation in nanoparticulate composition (abstract). The nanoparticulate composition comprising nanopaticulate drug and two or more surface stabilizers adsorbed to the surface of the drug (column 6, lines 45-59). Drugs comprise poorly soluble drugs (column 7, lines 4-31). Drugs are in crystalline or amorphous states (column 3, lines 41-50). Drug is used in an amount from about 99.9% to about 10% (column 9, lines 9-14). Surface active agents are disclosed in column 7, lines 39 through column 8, lines 1-36). Surface active agents are used in an amount of from about 0.1% to about 90% (column 9, lines 4-8). Liversidge further teaches the effective average particles size of the nanoparticle is at least about 95% of the particles have an average particle size of from about 150 nm to about 350 nm (column 8, lines 37-54). The nanoparticulate composition is suitable for parenteral administration in the form of dispersion, suspension or emulsion in aqueous or non-aqueous solutions (column 10, lines 4-34 and 55-67). The nanoparticulate composition also contains adjuvants such as preserving, wetting, emulsifying, and dispensing agents (column 10, lines 25-30).

Liversidge does not expressly teach the crystal growth inhibitor.

Straub teaches the use of sugar such as mannitol to inhibit crystal growth for drugs in an amorphous or crystalline state (paragraphs 0082-0083). Thus, it would

have been obvious to one of ordinary skill in the art to modify the nanoparticulate composition of Liversidge to include sugar to obtain the claimed invention. This is because Straub teaches the use of sugar as a bulking agent, wetting agent, or anti-crystallization agent to prevent crystal growth for drugs in crystalline state, because Straub teaches the use of mannitol to inhibit crystal growth for drugs in crystalline state is well known in the art, and because Liversidge teaches the desirability to prevent crystal growth for poorly soluble crystalline state drugs (column 3, lines 35-43), and because Liversidge teaches the use of other excipients in the nanoparticulate composition such as wetting agent. Therefore, one of ordinary skill in the art would have been motivated to combine surface modifiers, mannitol as an anti-crystallization, and nanoparticle drug with the expectation of additive affect in preventing crystal growth in nanoparticulate composition to obtain a nanoparticulate composition that exhibit prolonged particle size stability even following exposure to elevated temperatures.

Claims 25 and 30-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge US 6,267,989, in view of Straub et al. US 2002/0142050 A1 and Liversidge US 2005/0004049 (Liversidge '049).

Liversidge is relied upon for the reason stated above. The reference does not teach the claimed specific active agent suitable in a bioadhesive composition.

Liversidge '049 teaches a nanoparticulate composition comprising surface modifier, and a drug having solubility of less than about 30 mg/ml (abstract; and paragraph 0045). Drug including analgesic, NSAID and vitamins are discloses in paragraphs 0109-0113). The nanoparticulate composition is processed into a liquid

dosage for bioadhesive composition (paragraphs 0081-0089). Liversidge further teaches the claimed viscosity, Cmax, Tmax, and bioequivalency (paragraphs 0090-0105). Thus, it would have been obvious to one of ordinary skill in the art to modify the nanoparticulate composition of Liversidge to include active agents in view of the teaching of Liversidge '049 to obtain a useful bioadhesive composition of the present invention. This is because Liversidge '049 teaches the desirability to incorporate the claimed active agents in the nanoparticulate composition, and because Liversidge teaches a stable nanoparticulate composition suitable for a wide variety of active agents.

Claims 1-6, 8-10, 12, 14-15, 17, 21-24, 26-30 and 32-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bagchi et al., in view of De Garavilla et al. US 5,834,025 and Straub et al.

Bagchi is relied upon for the reason stated above. Bagchi does not explicitly teach the use of glycerol and mannitol in the composition.

Straub teaches the use of sugar such as mannitol to inhibit crystal growth for drugs in an amorphous or crystalline state (paragraphs 0082-0083).

De Garavilla teaches a nanoparticulate composition comprising the use of tow or more surface modifiers including glycerol (abstract; and column 9, lines 59-67).

Thus, it would have been obvious to one of ordinary skill in the art to modify the nanoparticulate composition of Bagchi to include sugar such as mannitol, and surface modifier including glycerol, in view of the teachings of De Garavilla and Straub. This is because Straub teaches the use of sugar as anti-crystallization agent to prevent crystal

growth for drugs in crystalline state, because De Garavilla teaches the use of glycerol as a surface modifier to prevent aggregation of drugs in nanoparticles size, because Bagchi teaches the use of crystal growth inhibitor, and because Bagchi teaches the use of surface modifier to minimizing the close, interparticle approach necessary for agglomeration and flocculation, thus obtaining a stable nanoparticulate composition.

Response to Arguments

Applicant's arguments filed 12/17/07 have been considered but are moot in view of the new grounds of rejection.

Applicant argues that as discussed in the prior response filed July 9, 2007, the increased bioavailability is achieved by decreasing the particle size of the active agent. *See,* for example, at page 1, lines 16-21; at page 4, lines 23-28; at page 5, lines 15-24; and at page 12, lines 3-10. By definition, "bioavailability" is a measurement of the rate and extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action (online Wikipedia encyclopedia). The skilled artisan would have appreciated that bioavailability is determined by a pharmacokinetic study and represented by the plasma drug concentration *vs.* time after administration. The specification further describes that bioequivalency "is preferably established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both Cm, x and AUC" (page 18, lines 18-25). Therefore, the specification provides written support that to achieve the claimed release profile, represented by the Cmax, Tmax, AUC and bioequivalency, the active ingredient must be reduced to an average particle size of less than 2000 nm

and be maintained stable at this size in the presence of at least one surface stabilizer and at least one osmotically active crystal growth inhibitor, as recited in claim 1. The specification is also enabling because it describes how to make nanoparticulate formulations (page 32*ff*) and how the composition is stabilized in the presence of different crystal growth inhibitors (Examples 1-8). Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

However, in response to applicant's argument, the issue here does not lie in the definition of the term "bioequivalent", but rather how the skilled artisan can obtain the specific pharmacokinetic profiles without any guidance or direction in view of multitude types of surfactants and crystal growth inhibitors. Moreover, the present specification clearly discloses that the pharmacokinetic profiles are desirable. No further showing as to how the "desirable" profiles can be achieved. Thus, it appears that the specific pharmacokinetic profiles are hypothetical. Accordingly, the 112, first paragraph rejection is proper.

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1618